REMARKS

Claim Rejection under 35 USC § 112

Claims 1-4 are rejected under 35 USC § 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner asserts that Claims 1-4 are indefinite because the variables represented by the R groups do not list all possible substituents which are included in the terms "substituted or unsubstituted".

The terms "substituted" and "unsubstituted" are commonly used terms of art, and are clear as written. It appears that the Examiner is objecting to the breath of the claims rather than the clarity or definiteness of the claims. The breath of the claims is not properly rejected under 35 USC § 112 second paragraph unless the Applicant has indicated that he intended the invention to be of a different scope than that defined in the claims (MPEP 2173.04):

> Breadth of a claims is not to be equated with indefiniteness. *In re Miller,* 441 f.2d 689, 169, USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear and if the applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

Since Applicant has not indicated that he intended the invention to be of a different scope than that defined in the claims, and the scope of the subject matter is clear, the rejection is not proper and withdrawal of the rejection is respectfully requested.

Further, the Applicant would like to point the Examiner to the composition claims of US Patent 6,969,728 which is under obligation of assignment to the same Assignee as the instant application (and the entire contents of which are incorporated by reference in the instant Application) (page 13 lines 22 – 24). The composition claims which issued in US Patent 6,969,728 (a copy of which is enclosed as Exhibit A) are directed to compounds represented by Formula (I) as in the instant method claims. Many of the R groups of the composition claims which issued in this patent are similar in scope to the claims of the instant Application. This would indicate that the United States Patent Office found these composition claims to be enabled and to comply with the written description requirement of 35 USC § 112 first paragraph.

The Examiner further rejects Claim 3, stating that "heteroaralkyl" as a possibility for the variable R_2 does not have antecedent basis in Claim 2. Applicant respectfully disagrees.

Claim 2 states that R_2 can be "an optionally substituted aralkyl group". The paragraph bridging pages 7 and 8 of the instant specification, defines an aralkyl to be:

> "...an alkyl group substituted with one or more aryl groups."

Page 7 lines 3 – 8 of the instant specification states that the term aryl group refers to:

> "...carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl, and heteroaryl groups such as imidazolyl..."

Therefore heteroaralkyl is a subgenus of aralkyl, and therefore there is sufficient antecedent basis for heteroaralkyl in Claim 3. Withdrawal of the rejection is respectfully requested.

The Examiner also states that there is insufficient basis for the terms "cycloalkyl, C1-C4 aralkyl and cycloalkylalkyl groups" as a possibility for the variable R_4 in Claim 4. Applicant again respectfully disagrees. Claim 2 states that R_4 can be "a substituted or unsubstituted alkyl group". An alkyl group is defined page 7, lines 19 – 29 as:

> "...a straight, branched or cyclic non-aromatic hydrocarbon"

Therefore, there is antecedent basis for cycloalkyl in Claim 4. Further, page 9, line 7 – 17 of the specification states that:

> "Examples of suitable substituents for a carbon atom of an aryl, alkyl or a carbon atom of a non-aromatic heterocyclic group include –OH, halogen (-Br, Cl, -I and –F), R..."

R is defined page 7 lines 18-19 as:

"...an alkyl, substituted alkyl, benzyl, substituted benzyl, aryl or substituted aryl group."

Therefore the term "substituted alkyl" includes an alkyl group substituted with aryl, i.e, an aralkyl, and includes an alkyl group substituted with alkyl, such as, a cycloalkyl group, i.e., a cycloalkylalkyl. Therefore, there is sufficient antecedent basis for the terms in Claims 4 and withdrawal of the rejection is respectfully requested.

Provisional Claim Rejection under the judicially created doctrine of Double Patenting

The Examiner provisionally rejects Claims 1-26 under the judicially created of double patenting over Claims 1-20 of co-pending Application No. 10/719,701.

As noted by the Examiner, the rejection is a provisional rejection because the claims of co-pending Application No. 10/719,701 have not been patented. Applicants will address the provisional double patenting rejection of Claims 1-26 in the subject application if the corresponding claims of co-pending U.S. Patent Application No. 10/719,701 are allowed or patented before the claims of the subject application.

If this provisional rejection is the only rejection remaining in either the subject application or co-pending Application No. 10/719,701 after entry and consideration of any Amendments, Applicants request that the Examiner withdraw the rejection and permit either the subject application or co-pending Application No. 10/719,701 to issue as a patent, in accordance with U.S. Patent Office procedure (see, M.P.E.P. § 804(I)(B)(1)).

Claim Rejection under 35 USC § 102 (b)

Claims 1-2, 4-8 and 12-15 are rejected under 35 USC § 102(b) as being anticipated by Sneddon *et al.,* WO 01/87849.

35 USC § 102(b) states:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this or a foreign country, more than one year prior to the date of the application for patent in the United States.

Sneddon *et al.*, (WO 01/87849) published on November 22, 2001, and the instant Application claims the benefit of provisional application 60/428,332 which was filed on November 21, 2002. Therefore Sneddon *et al.*, was not published more than one year prior to the filing of the instant Application and therefore is not properly rejected over Sneddon *et al.*, under 35 USC § 102(b).

Even if Sneddon *et al.*, would be prior art under 35 USC § 102(b), the instant Claim are not anticipated by Sneddon *et al.*, for at least the following reasons:

The instant Claim 1 is directed to a method for inhibiting tissue transplant rejection in a subject, said method comprising the step of administering an effective amount of a compound represented by Formula (I) to the subject.

The instant Claims 2, 4-8 and 12-15 are directed to a method for inhibiting chronic tissue transplant rejection in a subject, said method comprising the step of administering an effective amount of a compound represented by Formula (I) to the subject.

Sneddon *et al.*, teach compounds which are modulators of TNFα signalling and methods of use thereof for treating a TNFα mediated condition in a subject. In making this rejection the Examiner states that Sneddon *et al.*, teach that TNFα mediated conditions include graft versus host disease and refers to the paragraph bridging page 14 and 15:

> Examples of TNF-α mediated conditions include, but are not limited to:
> (A) acute and chronic immune and autoimmune pathologies, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, thyroidosis, graft versus host disease, scleroderma, diabetes mellitus, Graves' disease, and the like;

According to The American Heritage Stedman's Medical Dictionary. Houghton Mifflin Company, 2002. *Answers.com* 17 Feb. 2006. http://www.answers.com/topic/graft-versus-host-disease (a copy of which is attached as Exhibit B) graft versus host disease is defined as:

> A type of incompatibility reaction of transplanted cells against host tissues that possess an antigen not possessed by the donor. Also called *graft versus host reaction.*

Therefore, graft versus host disease (GVHD) is not a typical host rejection of a tissue transplant; rather it is an unusual situation were the **graft cell attacks or rejects the host**. This type of

disease occurs typically in bone marrow transplants where the host is immunocompromised following radiation therapy.

While Sneddon *et al.,* have a generic teaching of a method of treating a TNFα mediated condition in a subject and a specific teaching of GVHD, Sneddon *et al.,* do not specifically teach that the compounds described therein can be used to inhibit a tissue transplant rejection. Therefore the instant claims are novel in light of Sneddon *et al.*

Further, Claims 2, 4-8 and 12-15 are directed to a method of inhibiting a **chronic** tissue transplant rejection in a subject comprising administering to the subject an effective amount of a compound represented by Formula (I). Chronic transplant rejection is a specific type of transplant rejection the underlying causes of which are not fully understood. Moreover, chronic transplant rejection may occur in patients who are being successfully treated for acute transplant rejection. The instant specification page 1 line 23 to page 2 line 5 states:

> Whereas acute rejection is suppressed with immunosuppressive protocols, treatment for chronic rejection is less well defined. Acute rejection and chronic rejection have significantly different characteristics as immune responses. For example, chronic rejection occurs over time, typically several months to years after engraftment, even in the presence of successful immunosuppression. It involves multiple factors and processes of the host and is usually the result of a prolonged process of wound healing the host undergoes post-transplant. Therefore, chronic rejection is not totally immunological in origin and additional causes(s) are not fully understood. They may include ischemic insult, denervation of the transplanted tissue, hyperlipidemia and hypertension associated with immunosuppressive drugs.

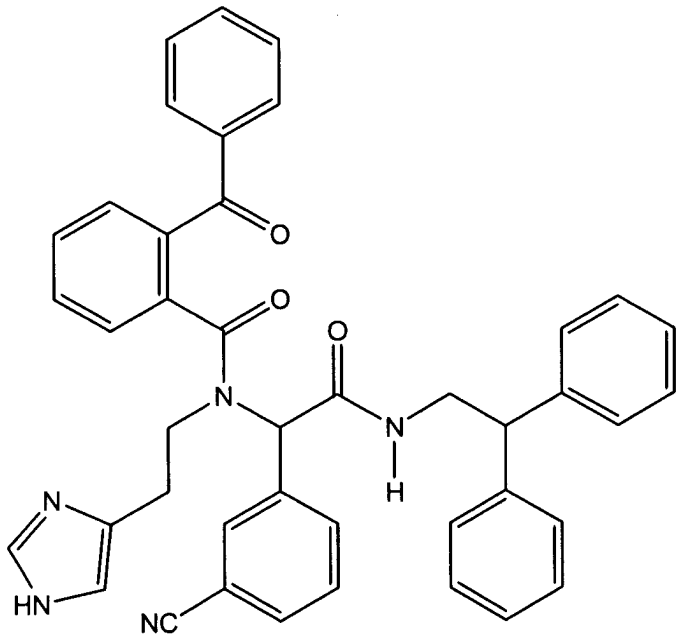
The above facts would indicate that it would not be obvious to one of skill in the art that one compound could be used to treat **both** acute and chronic transplant rejections, rather they would indicate that the opposite were true, that is, that different compounds would be required to treat the two different diseases.

Futhermore, there are currently no known treatments for chronic transplant rejection. The instant specification page 2 lines 19 - 20 states:

> The chronic rejection process is not inhibited by any known therapeutic regimen at this time.

The Applicant has now discovered that the compounds described in the instant specification are effective in preventing chronic transplant rejection. The instant specification page 2 lines 27 to page 3 line 12 states:

> In one example, the histopathological evidence of chronic rejection was inhibited in two mouse models by Compound **1**, shown below. In the first model, chronic rejection of fully MHC class II mismatched transplanted hearts in recipient mice at eight weeks post surgery was inhibited by treatment with 75 mg/kg/day of



Compound **1**

> Compound **1** alone during the two weeks following surgery. In the second model, chronic rejection of fully MHC class II mismatched transplanted hearts in recipient mice at 120 days post surgery was inhibited when treatment with 75 mg/kg/day of Compound **1** during the two weeks following surgery was combined with a single administration of 250 μg of anti-CD154 monoclonal antibody immediately following transplant surgery. Treatment with anti-CD154 monoclonal antibody alone suppresses acute rejection, but is ineffective in preventing chronic rejection of transplanted tissue.

In summation, while Sneddon *et al.*, have a generic teaching of a method of treating a TNFα mediated condition in a subject there is no specific teaching of treating chronic transplant

rejection. As discussed above, chronic transplant rejection is a specific type of transplant rejection, the underlying causes of which are not fully understood and for which there is currently no known treatment. The Applicant has discovered that the compounds described in the instant specification are effective in preventing chronic transplant rejection. Specifically, Applicant has found that the instant compounds inhibit chronic rejection of fully MHC class II mismatched transplanted hearts in recipient mice at eight weeks post surgery. Therefore, the instant invention represents a surprising and unexpected improvement in methods for inhibiting rejection of tissue transplants.

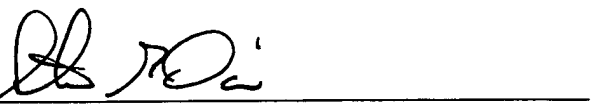
Sneddon *et al.*, not only do not provide a specific teaching of treating a tissue transplant rejection, they further do not provide a specific teaching of treating a **chronic** transplant rejection. Therefore the claims are novel and patentable in light of Sneddon *et al.*, and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Steven G. Davis
Registration No. 39,652
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: February 28 2006

graft-versus-host disease

Dictionary

The American Heritage® dic·tion·ar·ies

graft-ver·sus-host disease (grăft'vûr'sə-hōst', -sə-)
n.

A pathological condition in which cells from the transplanted tissue of a donor initiate an immunologic attack on the cells and tissue of the recipient.

Cancer Dictionary

THOMSON GALE

Graft versus host disease

After bone marrow transplant, the newly transplanted white blood cells can attack the patient's own tissues.

Medical

HOUGHTON MIFFLIN COMPANY

graft-versus-host disease
n.

A type of incompatibility reaction of transplanted cells against host tissues that possess an antigen not possessed by the donor. Also called *graft versus host reaction*.

Wikipedia

Graft-versus-host disease

Graft-versus-host disease is a common complication of allogeneic bone marrow transplantation. After bone marrow transplantation, T cells present in the graft, either as contaminants or intentionally introduced into the host, attack the tissues of the transplant recipient. Graft-versus-host disease can occur even when HLA-identical siblings are the donors. HLA-identical siblings or HLA-identical unrelated donors (called a minor mismatch as opposed to differences in the HLA antigens, which constitute a major mismatch) often still have genetically different proteins that can be presented on the MHC.

While donor T-cells are undesirable as effector cells of graft-versus-host-disease, they are valuable for engraftment by preventing the recipient's residual immune system from rejecting the bone marrow graft (host-versus-graft). Additionally, as bone marrow transplantation is frequently used to cure malignant disorders (most prominently the leukemias), donor T-cells have proven to have a valuable graft-versus-tumor effect. A great deal of current research on allogeneic bone marrow transplantation involves attempts to separate the undesirable graft-vs-host-disease aspects of T-cell physiology from the desirable graft-versus-tumor effect.

Types

Clinically, graft-versus-host-disease is divided into acute and chronic forms. The acute or fulminant form of the disease is observed within the first 100 days post-transplant, and the chronic form of graft-versus-host-disease is defined as that which occurs after 100 days. This distinction is not arbitrary: acute and chronic graft-versus-host-disease appear to involve different immune cell subsets, different cytokine profiles, and different types of target organ damage.

Classically, graft-versus-host-disease is characterized by selective damage to the liver, skin and mucosa, and the gastrointestinal tract. Newer research indicates that other graft-versus-host-disease target organs include the immune system (the hematopoietic system -- e.g. the bone marrow and the thymus) itself, and the lungs in the form of idiopathic pneumonitis. Chronic graft-versus-host-disease damages the above organs, but also causes changes to the connective tissue (e.g. of the skin).

Prevention

Graft-versus-host-disease can largely be avoided by performing a T-cell depleted bone marrow transplant. These types of transplants result in reduced target organ damage and generally less graft-versus-host-disease, but at a cost of diminished graft-versus-tumor effect, a greater risk of engraftment failure, and general immunodeficiency, resulting in a patient more susceptible to viral, bacterial, and fungal infection. Methotrexate and cyclosporin are common drugs used for GVHD prophylaxis. In a multi-center study (*Lancet* 2005 Aug 27-Sep 2;366(9487):733-41), disease-free survival at 3 years was not different between T cell depleted and T cell replete transplants.

Bibliography

- *Graft-vs.-Host-Disease* by Ferrara et al. (2nd ed.) published by Marcel Dekker is somewhat out of date, but still a nice bound volume.
- Example journals that publish current research on graft-versus-host-disease include *The Biology of Blood and Marrow Transplantation, Journal of Clinical Investigation, Journal of Experimental Medicine, Blood, Journal of Immunology, Nature Immunology, Nature Medicine, Immunity,* and *Transplantation.*

See also

- Transplantation

  - Transplant rejection, also known as "host-verses-graft disease"
- Immunology
  - Immunosuppression
- Cancer

External links

- National Marrow Donor Program

This entry is from Wikipedia, the leading user-contributed encyclopedia. It may not have been reviewed by professional editors (see full disclaimer)

Donate to Wikimedia

Mentioned In

graft-versus-host disease is mentioned in the following topics:

Gell-Coombs classification	bone marrow (treatment — in anatomy)
Tacrolimus	aplastic anemia
bone marrow transplant	Cyclosporine
Diarrhea	Lymphocyte immune globulin
Bone marrow transplantation	Sirolimus
	More>

Tell me about: graft-versus-host disease